Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Objection to Claims 38-40

Claims 38-40 have been objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner suggests that the method claims of 38-40 do not further limit the composition of claim 34 and are thus improperly dependent. It is respectfully pointed out that the claims 38-40 have been canceled thus mooting this objection. Withdrawal of this objection is therefore respectfully requested.

II. Rejection of Claims 11, 35-43 and 45-59 under 35 U.S.C. § 112, first paragraph

Claims 11, 35-43 and 45-59 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At the outset, it is respectfully pointed out that claim 11

has been canceled thus mooting the rejection as it pertains to this claim.

With respect to claims 35-43 and 45-58, the Examiner suggests that the specification is non-enabling because insufficient guidance is provided with respect to how to identify all neurological or neurodegenerative diseases which can be successfully treated with neuron-restricted precursor cells, how to determine effective amounts of the cells for all neurological or degenerative diseases, and how to target the cells to appropriate sites such that the cells are effective in treating the neurological or neurodegenerative disease.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended the claims to specify the neurological or neurodegenerative diseases, conditions or disorders which can be treated with neuron-restricted precursor cells of the present invention. Support for this amendment can be found in the specification at page 24, line 21 through page 25, line 2. Further, Applicants have amended the claims to clarify that the NRP cells are transplanted into mammals suffering from these disorders at or near any regions of the central nervous system (CNS) affected by these diseases or conditions. Support for this amendment can be found in multiple places throughout the specification. See for

example, page 16, where effective amounts of cells for transplantation are defined; page 17 wherein the phrase "administering an NRP cell" is defined to mean transplanting or implanting such NRP cells into the CNS or adjacent to the CNS; page 58 where transplantation of cells into animals is outlined; and Example 20 beginning at page 61 where a protocol for transplantation of NRP cells into humans is provided.

Guidance for determining effective amounts of cells to be transplanted in the claimed neurological or degenerative diseases is provided in the specification at page 16, beginning at line 16. Ranges for concentrations of cells to be administered and specific volumes of cells which can be transplanted are both taught. Details regarding effective amounts of cells to be transplanted are also described in Example 20, beginning at page 61. Guidance is also provided beginning at page 58 and also in Example 20 with respect to transplanting cells at appropriate sites such that the cells are effective in treating neurological or neurodegenerative diseases.

Accordingly, the instant specification provides sufficient guidance to make and/or use the invention as now set forth in the amended claims. Withdrawal of the rejection of claims 35-43 and 45-58 is therefore respectfully requested.

With respect to claim 59, which is drawn to a method of isolating a pure population of mammalian CNS neuron-restricted precursor cells which requires a sample of mammalian embryonic stem cells, the Examiner suggests that there is no specific deposit number of the mouse ES cells disclosed in the specification and that the specification does not provide guidance as to how to obtain embryonic stem cells from other species. As acknowledged by the Examiner, the specification does teach at page 55 that mouse ES cells were obtained from the Developmental Studies Hybridoma Bank (DSHB). The Deposit Number for the specific mouse ES cells used in Example 18 is ES D-3. It is respectfully pointed out, however, that there is only one other mouse ES cell line deposited in DSHB which behaves identically to that exemplified in the instant specification. Further, Thompson et al. have shown neuronal differentiation in human ES cells (Science 1998). Thus, one of skill in the art would know from the prior art how to obtain ES cells for use in the instant invention at least in humans. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 59 to be drawn to mouse or human ES cells. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is therefore respectfully requested.

III. Rejection of Claims 1-59 under 35 U.S.C. § 112, first paragraph

Claims 1-59 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner has acknowledged the specification to be enabling for isolating a homogeneous population of a rat neuron-restricted progenitor cell. However, the Examiner suggests that the specification does not reasonably provide enablement for isolating a homogeneous population of any mammalian neuron-restricted progenitor cells. Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's suggestion that the specification is enabling only for rat neuron-restricted progenitor cells. It is stated at page 18, lines 3-4, that the present invention is illustrated using neuron-restricted precursor cells isolated from rats, mice and humans. Further, NRPs from mice are described in Example 17 beginning at page 54 and NRPs from humans are described in Example 19 beginning at page 56. Thus, in an earnest effort to advance the prosecution of this case, Applicants have amended the pending claims to be drawn to rodent and human NRP cells in accordance with the specific examples provided in the specification. Withdrawal of this rejection is therefore respectfully requested.

IV. Rejection of Claims 1-59 under 35 U.S.C. § 112, second paragraph

Claims 1-59 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In an earnest effort to advance the prosecution of this case, Applicants have made multiple amendments to more definitively claim the instant invention. However, Applicants respectfully disagree with many of these rejections.

MPEP § 2173.02 states that definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application; (B) The teachings of the prior art: and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. What is meant by much of the claim language suggested by the Examiner to be indefinite would be quite clear to one possessing an ordinary level of skill in this art when read in light of the teachings of the instant application and the prior art.

Specifically, with respect to the Examiner's rejections of claims 1, 2, 3, 7, 8-11, 17, 20, 34, 35, 36, 39, 41, 42 and 46-48 it is respectfully pointed out that these claims have been canceled

thus mooting this rejection as it pertains to these claims.

Claim 12 is suggested to be vague and indefinite for inclusion of the phrase "capable of" and because it is unclear from what source the population of mammalian multipotent CNS stem cells are obtained; how the cells are isolated; what the characteristics of the multipotent stems cells are such that the cells can be identified as precursors/progenitors of neurons and glia; what ingredients are present in the medium prior to the purification recited in step (c); what process steps are required for the purification of the cells in step (c); what selected antigen would suitably define the cells as neuron-restricted precursor cells; and what type of medium and what culture conditions are required to support adherent cell growth. In addition, the Examiner suggests that there is a step missing as it is unclear at which point in the method the pure population of mammalian CNS neuron-restricted precursor cells is isolated.

Accordingly, in an earnest effort to advance the prosecution of this case, claim 12 has been amended to remove the phrase "capable of" and to clarify that the multipotent stem cells are from rodents or humans as taught in the specification at page 18, lines 3-4, Example 17 beginning at page 54 and Example 19 beginning at page 56. Further, claim 12 has been amended to specify that the

medium prior to the purification is NEP medium as taught at page 22; to specify the processes which can be used to purify the cells in step (c) as set forth in claim 14, now canceled; and to specify that the selected antigen defining the cells as neuron-restricted precursor cells is embryonic neural cell adhesion molecule as set forth in claim 13, now canceled. In addition, the claim has been amended to clarify at which step the isolated, purified population of NRP cells is obtained. However, characteristics of multipotent stems cells which enable one of skill in the art to identify them as precursors/ progenitors of neurons and glia, as well as the types of medium and culture conditions required to support adherent cell growth, are well known in the art. Accordingly, claim 12 as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

Claim 21 is also suggested to be vague and indefinite because it is unclear if any portion of the CNS tissue can be used in the method; it is unclear which selected antigen, substratum, medium, temperature and atmosphere are required for isolating the neuron-restricted precursor cells and supporting growth of the cells. In addition, the Examiner suggests that the claim is incomplete as there is no process step in which the neuron-restricted precursor cells are recovered for isolating the pure population of neuron-

restricted precursor cells as set forth in the preamble.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 21 to clarify that the selected antigen is embryonic neural cell adhesion molecule as set forth in claim 22, now canceled. Claim 21 has also been amended to clarify that the CNS tissue is spinal cord tissue in accordance with teachings throughout the specification. See e.g., page 19-20, and Examples 1 and 2. In addition, claim 21 has been amended to clarify at which point the cells are isolated in accordance with the preamble of the claim. With respect to the substratum, medium, temperature and atmosphere required for isolating the neuron-restricted precursor cells and supporting growth of the cells, however, Applicants respectfully disagree that these terms require further definition. Multiple examples of substratum are taught in the instant application. In addition methods for determining the types of medium, temperature and atmospheric conditions which support cell growth are well known to those skilled in the art and can be identified routinely in accordance with the teachings of this specification. Accordingly, claim 21 as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

Claim 28 is also suggested to be vague and indefinite because it is unclear how the cells are provided and it is unclear what

types of conditions are proliferating or differentiating conditions. The Examiner also suggests that the claim is incomplete because there is no process step in which the postmitotic neurons are recovered for obtaining postmitotic neurons as set forth in the preamble.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 28 to clarify that this is a method of producing postmitotic neurons rather than obtaining, thus mooting the Examiner's comments relating to a missing process step for obtaining the cells. Further, Applicants have deleted the phrase "providing neuron-restricted precursor cells" which was suggested to be vague by the Examiner. With respect to the Examiner's suggestion that proliferating and differentiating conditions are vague, it is respectfully pointed out that such conditions are described in detail throughout the specification; see for example, page 10, lines 14-19 wherein various differentiating conditions are described. Clearly, when one reads the terms proliferating and differentiating conditions in light of the content of this application as required under MPEP § 2173.02, what is meant is quite clear. Thus, claim 28, as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

Claim 37 is suggested to be vague and indefinite as it is

unclear how a neuronal disorder is defined. Further, the Examiner suggests that it is unclear if the mode of administering is dependent on the disorder being treated and if the "therapeutically effective amount" is dependent on the disorder being treated. Accordingly, claim 37 as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

Claim 37 has therefore been amended to define the neuronal disorders being treated, as taught at page 24, line 21 through page 25, line 2, and to define the mode of administration to be transplantation for which effective amounts are taught at page 16 and Example 20 of the specification.

Claim 43 is suggested to be vague and indefinite because it is unclear what type of neurodegenerative symptoms are intended, how the cells are genetically transformed, and whether the effective amount of cells to be administered is dependent on the symptoms being treated. Claim 58 is also suggested to be vague and indefinite because it is unclear what gene, promoter, regulatory sequences, expression vector, etc. are required for making the genetically transduced neuron-restricted precursor cells.

In an earnest effort to advance the prosecution of this case, Applicants have amended claim 43 to be dependent from claim 45 which specifically lists the type of neurodegenerative disorders

and diseases treated by transplantation of cells of the instant application. As discussed in Section II, *supra*, effective amounts of cells to be transplanted are described in various places throughout the specification.

Further, means for genetic transformation of the cells are described in the specification in Example 21. As discussed therein, various techniques for genetic modification are well known in the art. Thus, in accordance with MPEP § 2173.02, specific definition of the genetic modification technique in claim 43, or the gene, promoter, regulatory sequence, etc. in claim 58 is not required for these claims to meet the requirements of 35 U.S.C. § 112, second paragraph.

Claim 44 is suggested to be vague and indefinite for the phrase "monitoring the reaction" because it is unclear what type of reaction should be monitored. It is respectfully pointed out that Example 22 of the instant specification describes in detail reactions of the NRP cells, or derivatives or mixtures thereof to be monitored in these screening assays. Thus, contrary to the Examiner's suggestion, what it encompassed by the phrase "monitoring the reaction" is clear to one of skill in the art when read in light of the specification as required by MPEP § 2173.02.

Claim 45 is suggested to be vague and indefinite for the

phrase "neurological or neurodegenerative disease" because it is unclear which diseases are intended and it is unclear if the effective amount of cells to be administered is dependent on the disease being treated. As discussed in Section II, *supra*, claim 45 has been amended to specify the neurological or neurodegenerative diseases to be treated via the instant invention and that the mode of administration is transplantation for which effective ranges of cells to be administered are taught. Thus, claim 45, as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

Claims 44-49, 53 and 57 are suggested to be vague and indefinite for the term "derivative" as it is unclear what a derivative of a neuron-restricted precursor cell encompasses. It is respectfully pointed out that the term "derivative" is defined in the specification at page 17, lines 3-4, and means "a cell derived from an NRP cell *in vitro* by genetic transduction, differentiation or similar processes. Thus, what is meant by this term in the claims is clear when read in light of the teachings of the specification as required by MPEP § 2173.02 and further definition in the claims is not required.

Claim 59 is suggested to vague and indefinite because it is unclear which selected antigen, substratum, medium, temperature and atmosphere are required for isolating the neuron-restricted

precursor cells and supporting growth of the cells. Accordingly, claim 59 has been amended to specify that the antigen is embryonic neural cell adhesion molecule. As discussed previously, however, selection of a substratum, medium, temperature and atmosphere is performed routinely by those skilled in the art in accordance with teachings provided in the specification and need not be defined specifically in the claims. Accordingly, claim 59 as amended meets the requirements of 35 U.S.C. § 112, second paragraph.

In addition, the Examiner suggests that the phrase "neuron-restricted precursor" and "neuronal restricted precursor" appear to be used interchangeably. Thus, the Examiner suggests that it is unclear whether the two phrases are identifying one or two cell populations. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended the pending claims to all identify the cell population as neuron-restricted precursor cells.

Withdrawal of these rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested in light of amendments made to the claims and the above arguments.

V. Rejection of Claims 1-10, 21-23, 25-27 and 34 under 35 U.S.C. § 102(b)

Claims 1-10, 21-23, 25-27 and 34 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Blass-Kampmann et al. (J. Neuroscience Research 37:359-373 1994. The Examiner suggests that the cells of Blass-Kampmann et al. have the same phenotypic and morphologic characteristics of the claimed cells. Applicants respectfully disagree.

With respect to claims 1-10, it is respectfully pointed out that these claims have been canceled, thus mooting this rejection as it pertains to these claims.

With respect to other claims included within this rejection, Applicants are providing herewith a Declaration by Dr. Mahendra Rao which contains a detailed explanation supported by the teachings of the instant application and those of Blass-Kampmann et al. of the differences in characteristics between the cell population of the instant invention and that taught by Blass-Kampmann et al. As discussed in Dr. Rao's Declaration, the cells taught by Blass-Kampmann et al. differ from those of the instant invention in their ability to differentiate into glial cells, their growth factor requirements and their survival times. Specifically, as discussed in paragraph 4 of Dr. Rao's Declaration, Blass-Kampmann et al.

teach that their cells differentiate into both neurons and astrocytes which are glial cells. In contrast, as also discussed in paragraph 4 of Dr. Rao's Declaration, the cells of the instant invention do not differentiate into glial cells including astrocytes even under conditions known to promote astrocyte differentiation. In addition, as discussed in paragraphs 5 and 6 of Dr. Rao's Declaration, the cells taught by Blass-Kampmann et al. grow on 10% FCS and do not require FGF. However, as discussed in paragraph 5 of Dr. Rao's Declaration, the cells of the present invention die when grown of FCS. Further, as discussed in paragraph 6 of Dr. Rao's Declaration, the cells of the present require FGF for growth. Finally, as discussed in paragraph 7 of Dr. Rao's Declaration, the cells taught by Blass-Kampmann die after three days while the cells of the present invention grow over multiple passages.

In an earnest effort to clearly distinguish the cell population of the present invention from that taught by Blass-Kampmann et al. Applicants have amended pending claims to clarify that the cell population requires FGF and differentiates into CNS neuronal cells but not into CNS glial cells. Support for this amendment can be found in original claim 3, now canceled and in the specification in Examples 3, 4 and 5. In contrast, the cells

taught by Blass-Kampmann do not require FGF and differentiate into neuronal and glial cells. See paragraphs 4 and 6 of Dr. Rao's Declaration. Thus, the cell population of the instant invention as now claimed is clearly different from the cells taught by Blass-Kampmann et al. Withdrawal of this rejection is therefore respectfully requested.

VI. Rejection of Claims 12-20, 24, 28-33 and 44 under 35 U.S.C. § 103(a)

Claims 12-20, 24, 28-33 and 44 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Blass-Kampmann et al. taken with Boss et al. (U.S. Patent 5,411,883), Weiss et al. (WO93/01275, 1993), Johe et al. (U.S. Patent 5,753,506), Rao et al. 26th Annual Meeting of the Society for Neuroscience, 22:527, Abstract #215.12, 1996) and Lee et al. (U.S. Patent 5,175,103). The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the cell culture methods of Boss et al., Weiss et al., or Johe et al. by isolating specific populations of lineage restricted cells, such as those disclosed by Blass-Kampmann et al. to determine the effect of different *in vivo* developmental stages

on the ability of precursor cells to differentiate into various cell types of the central nervous system, and to determine the effect of various growth factors, such as fibroblast growth factor and chick embryo extract, as disclosed by Rao et al. or different maturation factors, as disclosed by Boss et al., Weiss et al., or Johe et al., or different substrate, as disclosed by Lee et al., for directing the precursor cells into different lineages. The Examiner suggests that in view of the combined teachings, one of ordinary skill in the art would have had a high expectation of successfully obtaining neuronal cells at a specific stage of differentiation by isolating the neuronal cells during the claim-designated stages of *in vivo* development, using an antibody which binds to a cell surface marker expressed during that particular stage of differentiation, such as embryonic neural cell adhesion molecule, prior to or after culturing, using any of the claim-designated isolation protocols absent evidence to the contrary. Therefore, the Examiner suggests that it would have been obvious to one or ordinary skill in the art to isolate a population of neuronal precursors, expand the precursors *in vitro* under the appropriate cell culture conditions, and differentiate the cells into neurons as these cells can be utilized to study various aspects of neural cell biology.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The cited combination of prior art fails to meet these three criteria.

As discussed in detail in Section V, *supra*, the pending claims have been amended to clarify that the cell population requires FGF and differentiates into CNS neuronal cells but not into CNS glial cells. None of the prior art references teach or suggest a cell population with these characteristics.

The primary reference cited in this obviousness rejection by Blass-Kampmann et al. teaches cells which do not require FGF and which differentiate into both neurons and glial cells, specifically astrocytes. Accordingly, the primary reference does not teach or suggest all the limitations of the claims as amended.

Further, the secondary references cited by the Examiner in this rejection fail to remedy the deficiencies in the teachings of

the primary reference.

The teachings of Boss et al. and the differences between the cells of the present invention and those of Boss et al. are discussed in detail in paragraphs 9 through 11 of Dr. Rao's Declaration. As discussed in paragraph 9 of Dr. Rao's Declaration, the cells taught by Boss differentiate into different neurons and have different growth factor requirements from the cells of the present invention. Specifically, the mesencephalic cells of Boss et al. differentiate into dopaminergic neurons (see paragraph 10 of Dr. Rao's Declaration). Further the cells of Boss et al. do not require FGF (see paragraph 11 of Dr. Rao's Declaration). Accordingly, Boss et al. also fails to teach or suggest the claimed invention as amended.

Weiss et al. teach cells derived from the neural tube that give rise to both neurons and glia. Thus, this reference also fails to teach or suggest cells which differentiates into CNS neuronal cells but not into CNS glial cells as claimed.

Johe et al. (U.S. Patent 5,753,506) describe a nestin immunoreactive stem cell with some similar properties to cells claimed in the instant application in that they undergo self renewal and can differentiate into neurons. However, like the cells of Weiss et al., these cells also differentiate into

astrocytes and oligodendrocytes upon culture in appropriate differentiation conditions. Thus, this reference also fails to teach or suggest cells which differentiates into CNS neuronal cells but not into CNS glial cells.

Rao et al. discloses NEP cells which are stated in the Abstract to generate all major CNS cell types in culture. Thus, the NEP cells of Rao et al. are also different from the NRP cells claimed in the instant application.

Finally, the teachings of Lee et al. relate to cells which are derived from a human teratocarcinoma cell line which are different from the cells of the instant application.

Thus, this combination of references fails to provide the requisite teaching or suggestion of all the limitations of the claims as amended to render the invention *prima facie* obvious.

Further, contrary to the Examiner's suggestion, at the time of this invention, those of ordinary skill in the art had no expectation of successfully obtaining neuronal cells of the instant application. There is an important distinction between methods for obtaining neurons (such as that described by Weiss et al., Johe et al., Lee et al. and others), and obtaining dividing neuronal precursors as in the present invention. As discussed in paragraph 12 of Dr. Rao's Declaration, neurons can be obtained from cell

populations via methods such as those taught by Weiss et al., Johe et al., Rao et al. and Lee et al. However, dividing neuronal precursors that differentiate solely into neurons had not been shown to develop from any of the cell populations described in the art. In fact, there was doubt to the existence of such cells until the present invention. See paragraph 12 of Dr. Rao's Declaration and references cited and provided therein which evidence the fact that one of skill did **NOT** have **ANY** expectation of isolating the cells of the instant application.

Withdrawal of this obviousness rejection is therefore respectfully requested.

VI. Double Patenting Rejection of Claims 1-7, 12-16, and 28-32

Claims 1-7, 12-16 and 28-32 of this application are suggested to conflict with claims 1-12 and 24-26 of Application No. 08/909,435. It is respectfully pointed out that claims 1-7 of the instant application have been canceled while claims 8-29 of copending application No. 08/909,435 have been canceled. Accordingly, claims coextensive in scope are no longer pending in these applications. Withdrawal of this rejection is therefore respectfully requested.

VII. Obviousness-type Double Patenting Rejection

Claims 8-11, 17-29, 33 and 34 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-23 and 27-29 of copending Application No. 08/909,435. However, it is respectfully pointed out that claims 13-23 and 27-29 are no longer pending in copending Application No. 08/909,435. Accordingly, withdrawal of this rejection is respectfully requested.

VIII. Sequence Compliance

The Examiner suggests that this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825. Specifically, the Examiner suggests that the application does not contain as a separate part of the disclosure a paper copy of a sequence listing as required by 37 C.F.R. 1.821(c). Further, the Examiner suggests that a computer readable form was not submitted as required by 37 C.F.R. 1.821(e).

Applicant are providing herewith a copy of the stamped return post card evidencing the fact that a paper copy and computer readable form of the Sequence Listing were provided with the application upon filing. Applicants are also providing herewith a replacement paper copy, computer readable form of the Sequence

Listing, and a Statement to support the submission of this replacement Sequence Listing. This replacement sequence Listing contains identical sequence information to that submitted with the application upon filing. However, information relating to the application Serial No. and filing date and the program in which the Sequence Listing was generated have been updated. No new matter has been added in this replacement Sequence Listing.

IX. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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